

Remarks

Reconsideration of this Application is respectfully requested. Claims 47-63, 106 and 107 are pending in the application, with claim 47 being the independent claim. Support for the amendment to claim 48 may be found throughout the application and, in particular, on page 26, lines 8-14. Support for new claims 106 and 107 may be found throughout the application and, in particular, on page 20, lines 25-27. No new matter has been added by way of these amendments.

I. Summary of the Office Action

In the Office Action dated February 13, 2003, the Examiner rejected claims 47-63. Applicants respectfully offer the following remarks to overcome each of the Examiner's rejections.

II. Rejections under 35 U.S.C. § 112, Second Paragraph

In the Office Action, page 3, section 5, claim 47 was rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite with respect to the phrase "one or more cDNA molecules or a population of cDNA molecules." Applicants respectfully traverse this rejection.

The specification contains the following passages that demonstrate the difference between "one or more cDNA molecules" and "a population of cDNA molecules."

If cDNAs are prepared from a number of different mRNAs, the resulting set of cDNAs is called a "cDNA library," an appropriate term since the set of cDNAs represents a "population of genes or

portions of genes comprising the functional genetic information present in the source cell, tissue or organism. Specification at 2-3.

In a preferred aspect, a population of mRNA molecules (a number of different mRNA molecules) are used to make a cDNA library according to the present invention. Specification at 18.

Both excerpts show that the term "population" is used to describe a group of nucleic acid molecules suitable for the production of a cDNA library, a meaning that is routinely applied to the term by persons of ordinary skill in the art. By contrast, the term "one or more cDNA molecules" includes a potentially low number of different nucleic acid molecules. Thus, the specification provides a clear distinction between the terms "one or more cDNA molecules" and "a population of cDNA molecules." Therefore, Applicants respectfully request that the rejection of claim 47 under 35 U.S.C. § 112, second paragraph, be withdrawn.

In the Office Action, at page 3, section 6, claims 47, 52 and 53 were rejected for allegedly being indefinite with respect to the difference between "reduce" and "substantially reduce." Applicants respectfully traverse this rejection.

The use of the term "substantially" gives flexibility to the term it modifies, but it does not necessarily render a claim indefinite. *See* MPEP 2173(b)(D) (Rev. 1, Feb. 2003); *See also In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975); *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988).

When interpreting claim terms, one starts with the plain and ordinary meaning of the words and with intrinsic evidence, *i.e.* the teachings and definitions of the specification. The ordinary meaning of the term "reduced" is "lessened," and this meaning is reflected in the usage of the term throughout the specification. In addition, the specification contains the following passage:

By an enzyme "substantially reduced in RNase H activity" is meant that the enzyme has less than about 30%, less than about 25%, less than about 20%, more preferably less than about 15%, less than about 10%, less than about 7.5%, or less than about 5%, and most preferably less than about 5% or less than about 2%, of the RNase H activity of the corresponding wildtype or RNase H⁺ enzyme. . . . Specification at 21-22.

Thus, not only does the ordinary meaning of the terms "reduced" and "substantially reduced" enable the ordinary artisan to differentiate between them, but the paragraph above presents to the artisan a defined range of values for what constitutes a "substantially reduced" parameter. Therefore, Applicants respectfully request that the rejection of claims 47, 52 and 53 under 35 U.S.C. § 112, second paragraph, be withdrawn.

In the Office Action, on page 3, section 7, claims 48 and 49 are rejected as these claims allegedly "are confusing as to just what type of "fragment" of an antibody need be present." Applicants respectfully traverse this rejection, and direct the Examiner's attention to the following passage in the specification:

As used herein, the term "antibody" (Ab) may be used interchangeably with the terms "polyclonal antibody" or "monoclonal antibody" (mAb), except in specific contexts as described below. These terms, as used herein, are meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')₂ fragments) *which are capable of specifically binding to a polypeptide having reverse transcriptase activity* (such as a DNA polymerase or a reverse transcriptase) or cap structures or portions thereof. Specification at 26-27 (emphasis added).

In the interest of expediting the allowance of the above-captioned application, Applicants have amended claim 48 to more clearly point out and claim the subject matter of the invention. Applicants respectfully request that the rejection of claims 48 and 49 be withdrawn.

In the office Action, at page 3, section 8, claim 50 was rejected on the basis that the term

"low" is allegedly a relative term that renders the claim indefinite. Applicants respectfully traverse this rejection.

The term "low" in claim 50 refers to the temperature at which an inhibitor of the currently-claimed invention inhibits reverse transcriptase activity. Applicants respectfully direct the Examiner's attention to the following passage in the specification:

Such reverse transcriptase inhibitors prevent or inhibit reverse transcriptase activity *at low temperatures* such that internal priming is prevented, inhibited, reduced or substantially reduced. In accordance with the invention, such inhibitors preferably prevent reverse transcriptase activity below 35°C, below 40°C, below 45°C, below 50°C, below 55°C, below 60°C, below 65°C, below 70°C, below 75°C, below 80°C, below 85°C and below 90°C. Depending on the thermostability of the enzyme having reverse transcriptase activity, the inhibitor may be designed to inhibit activity of the enzyme at a point at or near the temperature optimum. Specification at 7 (emphasis added).

Thus, a person practicing the invention as it is claimed and described in the above-captioned application, will have clear guidelines as to what the term "low" encompasses. Therefore, Applicants respectfully request that the rejection of claim 50 be withdrawn.

In the Office Action, at page 3, section 9, the Examiner rejected claims 55 and 56 as allegedly being indefinite for the inclusion of the term "about" in each of these claims. Applicants respectfully traverse this rejection.

The term "about" is used in conjunction with a temperature range. The courts have consistently held that the term "about," when used to modify a numerical range, does not render a claim indefinite. *See* MPEP 2173(b)(A) (Rev. 1, Feb. 2003); *see also W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Both claims recite a numerical range that is defined at both ends. Therefore, an ordinary artisan will have not difficulty in discerning whether the temperature range at which he is performing his experiment

falls within the scope of the claims. Applicants respectfully request that the rejection of claims 55 and 56 be withdrawn.

IV. Rejection under 35 U.S.C. § 103(a)

A. The References Cited by the Examiner Fail to Teach the Claimed Invention

In the Office Action, at page 4, section 13, the Examiner rejected claims 47-63 under 35 U.S.C. § 103(a) as being unpatentable over Scalice *et al.* (U.S. Patent No. 5,338,671) in view of Myers *et al.* ("Reverse transcription and DNA Amplification by a *Thermus Thermophilus* DNA Polymerase," *Biochemistry* 30:7661-7666 (1991)), Clontech (96/97 Catalog No. 5400-1 and 5400-2, p. 41 (1996)) and Odawara (U.S. Patent No. 5,989,819). Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination.

See In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, this burden has not been satisfied.

In one aspect, the claimed invention relates to conditions that reduce internal priming during reverse transcription and promote the production of full-length cDNA polynucleotide molecules. Such conditions may include the use of reverse transcriptase inhibitors, such as reverse transcriptase-specific antibodies. Scalice does not teach methods of reducing internal priming during reverse transcription, or methods of increasing the percentage of full-length cDNA polynucleotide molecules produced by reverse transcription. Nor does Scalice teach the use of reverse transcriptase inhibitors for any purpose. Thus, Scalice does not disclose, suggest, or otherwise contemplate the invention as claimed. Hence, Scalice is seriously deficient as a primary reference in the attempt to make out a *prima facie* case of obviousness.

The deficiencies of Scalice are not cured by the disclosures of Myers, Clontech and Odawara. Myers teaches that a recombinant DNA polymerase derived from the thermophilic eubacterium *Thermus Thermophilus* (Tth) possesses reverse transcriptase activity. However, like Scalice, Myers does not disclose, suggest or otherwise contemplate a method of the use of reverse transcriptase inhibitors to reduce internal priming. Thus, Myers does not cure the deficiencies in Scalice.

Clontech teaches the use of an antibody against Tth DNA polymerase as an inhibitor of nonspecific amplification and primer-dimer formation during *PCR* reactions. Thus, the Tth DNA polymerase-specific antibody mentioned in Clontech inhibits the DNA polymerase activity of Tth DNA polymerase. Nothing in Clontech suggests that the same antibody could inhibit the reverse transcriptase activity of this polymerase, or that this antibody could reduce internal priming during reverse transcription. In addition, Clontech does not disclose, suggest or otherwise

contemplate the use of the described antibody in reverse transcription reactions. Thus, like Myers, Clontech does not cure the deficiencies in Scalice.

Odawara teaches a method for quantitatively determining the presence of an antibody capable of inhibiting reverse transcriptase activity. Although Odawara discloses antibodies that inhibit reverse transcriptase activity, Odawara does not disclose a method of using such antibodies for the purpose of reducing internal priming. Therefore, Like Myers and Clontech, Odawara does not cure the deficiencies in Scalice.

In sum, because Scalice, Myers, Clontech and Odawara do not disclose, suggest, or otherwise contemplate the use of reverse transcriptase inhibitors to reduce internal priming in a reverse transcription reaction, these references, alone or in combination, do not teach or suggest all of the limitations of the invention as presently claimed. As such, under *Piasecki*, *Fromson*, *Fine* and *Dow Chemical*, a *prima facie* case of obviousness has not been established.

B. There is No Suggestion or Motivation to Combine the References

Applicants have established that the references cited by the Examiner fail to teach all of the elements of Applicants' claims. Therefore, it follows that a combination of the reference teachings would *not* lead one of ordinary skill in the art to Applicants' claimed invention. Notwithstanding this fact, Applicants also contend that neither the references themselves, nor the knowledge generally available to those of ordinary skill in the art, provide a suggestion or motivation to modify the cited references or to combine reference teachings.

The Examiner alleges that the skilled artisan would have the following motivation to combine the teachings of Scalice with the teachings of Myers, Clontech and Odawara:

In view of the teachings of the prior art of record, it would have been obvious to one of ordinary skill in the art at the time that the invention was made to have employed the use of an antibody that would have inhibited an RT as disclosed by Odawara in an assay to produce cDNA for as shown by Clontech and Scalice *et al.*, the application of such antibodies, one is able to reduce or eliminate the formation of nonspecific products. Accordingly, the ordinary artisan would have been both highly motivated to have used such antibodies and would have also had a most reasonable expectation of success. Office Action at 5.

This explanation appears to misapprehend where the required motivation must arise in order for a *prima facie* case of obviousness to be established. Applicants respectfully remind the Examiner that the requisite motivation for establishing a *prima facie* case of obviousness *must* be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See In re Kotzhab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). Moreover, the mere fact that an advantage *might* be realized by combining reference teachings does not mean that a skilled artisan would be motivated to do so. *See In re Mills*, 916 F.2d 680,682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1992) (Although a prior art device “may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so.”). In the present case, rather than pointing to anything specific in the references or in the general knowledge of those skilled in the art, the Examiner has simply asserted that the use of antibodies described in Odawara in assays mentioned in Clontech and Scalice will result in the reduction or elimination of nonspecific products. This assertion misses the point and does not provide the requisite motivation to combine the cited references. There is no dispute that the present invention is designed to reduce or eliminate nonspecific products -- indeed, the very goal of the present invention is to do just that. The real issue is the approach that is taken in producing such a method: the art (including Scalice) is silent about the use of

conditions that inhibit internal priming during *reverse transcription*. There is absolutely *nothing* in Scalice or any of the other cited references concerning the problem of nonspecific product generation during reverse transcription reactions or how one might solve such problems. Thus, the cited references would not have motivated one of ordinary skill in the art to achieve the present invention. Moreover, the Examiner has pointed to no acceptable objective evidence or sound scientific reasoning that would provide such motivation. Instead, the Examiner appears to *assume* that such motivation exists in the general knowledge, without providing any basis for such an assumption. As discussed above, the requisite motivation must be found either in the prior art or in knowledge that is generally available to those of ordinary skill in the art; a baseless *assumption* of such knowledge is legally impermissible under *Fine* and *Kotzhab*. Moreover, as the Federal Circuit has held:

[t]he range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not “evidence.”

In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999) (citations omitted). Because the Examiner has provided no actual evidence to support the conclusory statement that Scalice and the remaining references in combination render the present invention obvious, Applicants respectfully assert that a *prima facie* case of obviousness has not been established.

Therefore, it appears that the Examiner is attempting to find the required motivation to combine the cited references in Applicants’ own specification rather than in the cited art. As the Federal Circuit has held numerous times, however, such a hindsight analysis is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed

invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) (“When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself.”); *Fine*, 5 USPQ2d at 1600 (“One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.”); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant’s specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, “must be founded in the prior art, not in the applicant’s disclosure.”). The Board has also provided the same mandate on this issue:

it is impermissible to use the claimed invention as an instruction manual or “template” to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the use of hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima facie* case of obviousness.

V. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication could expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Version with markings to show changes made

48. (Once amended) The method of claim 47, wherein said inhibitor is an antibody or antibody fragment that inhibits said polypeptide.

Claims 106 and 107 have been added.